Introduction to Proliferation

Introduction

Much more than in other sections throughout our course, here in Proliferation, we focus on one of our fundamental mantras: "*Understanding is more important than truth.*" This lesson sets you up for the following four lessons. The way we organize the material does not make sense to a pathologist, to a cataloger of disease. The cell lines, the path from stem cell to mature cyte we discussed in General #3: *Hematopoiesis*, is such an obvious means of categorization and cataloging diseases of excess marrow proliferation. In fact, that is how many physiology textbooks organize their content and how any pathology textbook does it. But it doesn't make any sense, at all, for a person studying to practice medicine. The Proliferation series is mostly about cancer—leukemias, lymphomas, and plasma cell dyscrasias—but also includes a lesson on myeloproliferative disorders that don't always turn malignant.

You must be committed to our organization and simplification. We organized the basic science content of Proliferation to mirror the clinical lessons. We're orienting your learning now so your memory is arranged the way it needs to be accessed when you leave the basic sciences. We make drastic simplifications, eliminating potential overlap, to make the illness scripts, the diseases you learn, discrete, unique memories.

If you don't understand why these opening paragraphs are here, that's great. If you do, you know that what we are proposing will not be echoed in any textbook or external review resource. It's so different that to learn from us means learning only from us. It was super uncomfortable trying to fact-check this material, because every resource does it differently than we do it, and the same as every other resource. This way is better.

This lesson accomplishes a few things. First, we'll show you an easier way of approaching hematopoiesis—our four-tier method that eliminates the complexities of ST-HSC, CFUs, and BFUs. Second, we'll explore how and why everyone else categorizes the diseases the way they do, and then we'll show you our how and why. Third, we walk through, at a high level, each of the remaining four lessons, introducing vocabulary and orienting you to the content contained in each lesson. We do this mainly to prove to you that even though our material is arranged differently, you are still learning all you need to.

Simplified Hematopoiesis

The story told in General #3: *Hematopoiesis* is truth. Here we offer an easier, more clinical way to approach hematopoiesis.

There is a pluripotent **hematopoietic stem cell** (HSC) that expresses **CD34**. Only the pluripotent HSC expresses CD34. The HSC can divide and differentiate into one of two lineages. The lymphoid lineage is established by the HSC's dividing and differentiating its daughter into the **common lymphoid progenitor** (CLP). From the CLP, daughters divide and differentiate into either T cells or B cells. There is a dedicated blast for each cell type, a -blast eventually becoming a -cyte. Lymphoblasts become lymphocytes. NK cells are not considered. The myeloid lineage is established by the HSC's dividing and differentiating a daughter into a **common myeloid progenitor** (CMP). From that cell, daughters can become monocytes (from monoblasts), erythrocytes (from erythroblasts), thrombocytes (from megakaryoblasts), or any of the granulocytes (from myeloblasts). Megakaryoblasts-becoming-thrombocytes does not follow the blast-to-cyte nomenclature, but platelets (thrombocytes) do come from megakaryocytes. The one that really throws learners is the fact that the myeloblast can become any of the three granulocytes . . . or ALL three. Myeloblast to neutrophil/eosinophil/basophil doesn't follow the blast-to-cyte nomenclature, because these granulo-blasts become granulo-phils, not granulocytes. But whoops, that's just nomenclature magic because granulocytes just happened to be named for the

color they become, for what they are -philic for. In addition, it provides a useful clue. Only chronic myelogenous leukemia, a proliferation of myeloblasts, will show a basophilia. The only thing that causes a basophilia is malignancy.

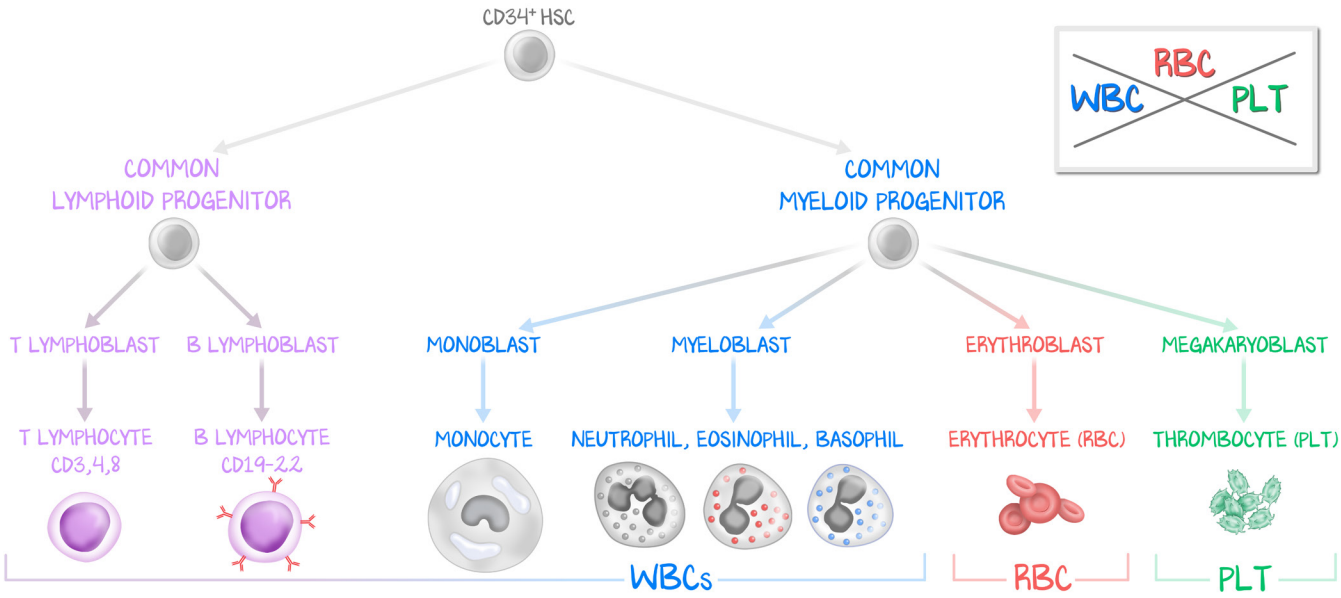

Figure 1.1: Simplified Hematopoiesis
See hematopoiesis as having four tiers. On the top tier is the hematopoietic stem cell. The second tier is the common progenitor, either lymphoid or myeloid. The third tier is a blast. That blast is named for the cell it will eventually differentiate into. A blast is one cell. It divides as it differentiates, so one blast becomes many mature cells, referred to as -cytes in general, or -phils if there are granules.

We've also kept the color-coding—white blood cells are blue, red blood cells are red, platelets are green, to match the video and previous lessons.

The Traditional Way vs. Our Way

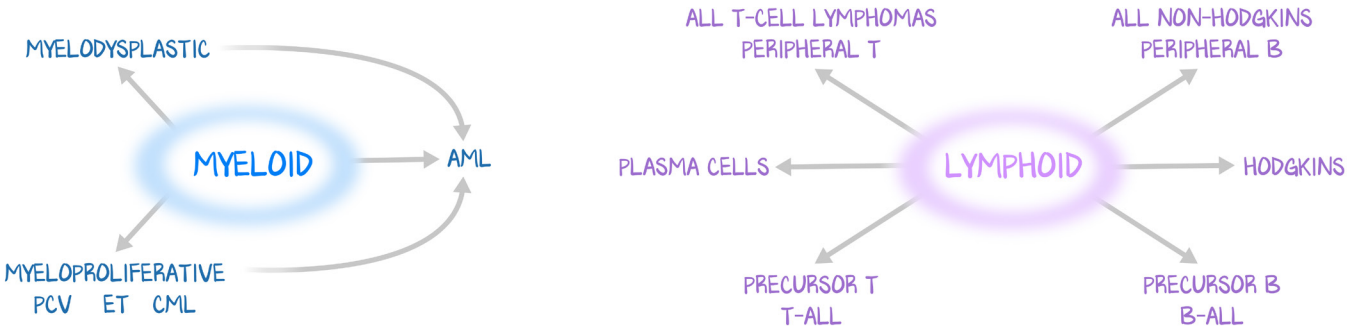

Figure 1.2: The Traditional Model
The traditional organization uses the progenitors within the pathway of hematopoiesis as the central organizing principle. This is appropriate for cataloging. It is not helpful for clinical practice. These disorders, at the tip of each arrow, are not related to one another by any feature other than the precursor they are made from.

The traditional method of organizing the diseases is a great way to organize white blood cell neoplasms when your goal is to catalog every possible cancer using hematopoiesis as the advanced organizer—all myeloid vs. all lymphoid. There are about 50 in Big Robbins in a table. But you know what doesn't work out when you consider a human being with a cancer? This organizational structure. Polycythemia vera is a disease of the myeloid progenitor, but has a different genetic cause (JAK2) and outcome (myelofibrosis) than CML, which is also a disease of the myeloid progenitor (cause: BCR-ABL; outcome: acute leukemia). So what we do is organize it in a way that makes more sense for you and for your patients, based on the presentation and pathogenesis.

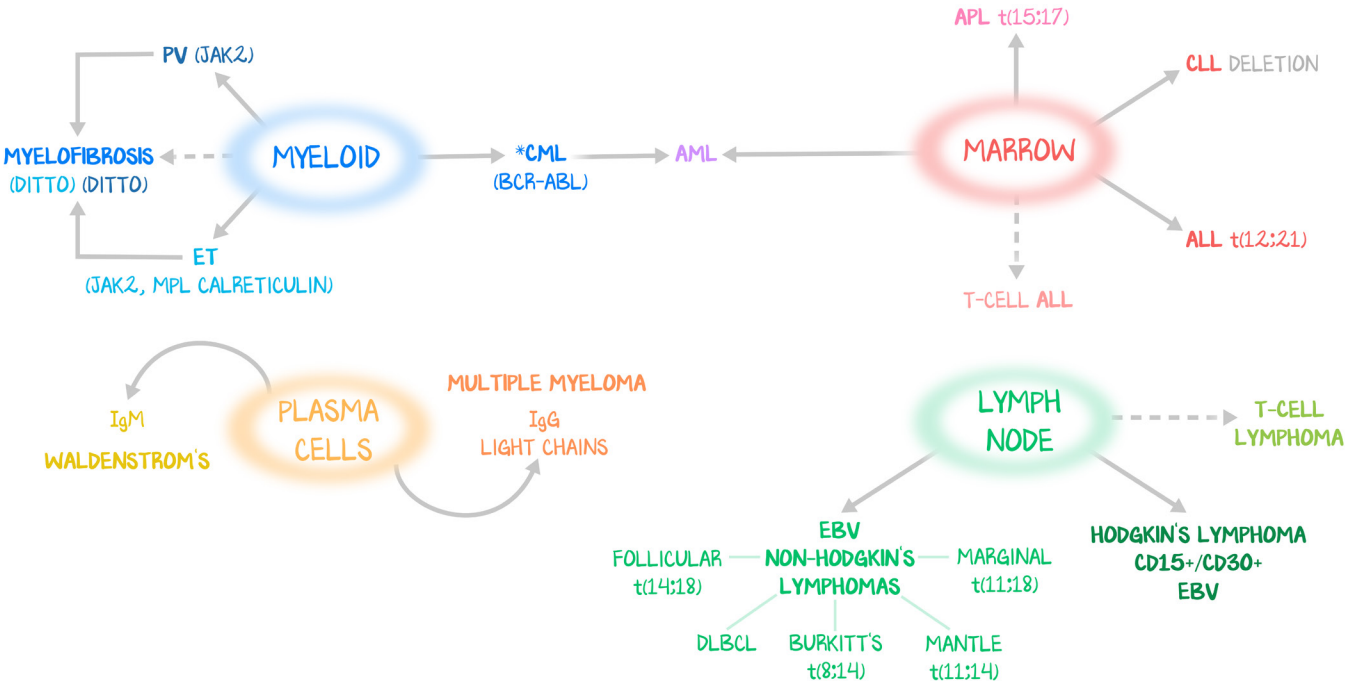

Figure 1.3: The OME Model
We take a different approach. There are the diseases of excess proliferation within the marrow (myeloproliferative disorders), diseases of the marrow that spill into the blood (leukemias), diseases that occur within secondary lymphoid organs (lymphomas, which we group with that organ), and diseases of plasma cells that secrete dysfunctional immunoglobulins (plasma cell dyscrasias). The only overlap is how we arrive at AML, either through a blast crisis of myeloproliferative disorders or as a spontaneous leukemia. Otherwise, this method separates all proliferation into four discrete categories, which map to four discrete lessons.

Feel this now. Proliferation #2: *Myeloproliferative Disorders* is about the diseases of excess platelets and excess red blood cells, caused by a mutation in JAK2 (or MPL or calreticulin), that initially increases the cellularity of the marrow and increases the numbers on the CBC, and usually results in myelofibrosis. In Proliferation #3: *Leukemia*, we conclude the discussion of the JAK/STAT pathway and BCR-ABL fusion protein while covering the leukemias. We cover the acute and severe blast versions, and the chronic and indolent mature versions. Leukemias—both lymphoid and myeloid—are discussed together because their presentations can be similar, though their pathogeneses are quite different. In Proliferation #4: *Lymphoma*, we tackle Hodgkin's lymphoma and the non-Hodgkin's lymphomas, with honorable mention to T-cell lymphomas. Hodgkin's has its own pathogenesis ($CD15^+/CD30^+$) and is found in the lymph nodes. Non-Hodgkin's varieties involve gene rearrangements during isotype switching, translocating the Ig heavy-chain gene with another protein that promotes proliferation or at least anti-apoptosis, and is found in the lymph nodes. The presentation of being in the lymph nodes is why HL and NHL are discussed together, how you'll actually see a patient—with a swollen lymph node.

Finally, in Proliferation #5: *Plasma Cell Dyscrasias*, we address the range of severity of multiple myeloma, which secretes IgG or Ig light chains, and lymphoplasmacytic lymphoma (also known as Waldenstrom's macroglobulinemia), which secretes IgM. We link the plasma-cell-secreting immunoglobulins together.

The remainder of this lesson is a high-level overview of the Proliferation series, with the must-know takeaways highlighted.

Lesson #2: Myeloproliferative Disorders

Myeloproliferative disorders are the disorders of myeloid cell lines that increase the proliferation of those lines. In all cases, there is some mutation that results in excess proliferation. The mutation is acquired by a progenitor. It does what it is supposed to do when stimulated to proliferate—it divides and differentiates its daughter. Which cell line predominates is how we name the disease. When the progenitor spawns more red blood cells than other cell lines, it is called polycythemia vera and is associated with a JAK2 mutation. When the progenitor spawns more platelets than other cell lines, it is called essential thrombocytosis (also essential thrombocythemia, both abbreviated ET) and is associated with either a JAK2 or MPL mutation. If that progenitor spawns more neutrophils than other cell lines, it is called chronic myelogenous leukemia and is associated with the BCR-ABL fusion protein. JAK2, MPL, and BCR-ABL all induce proliferation through the JAK/STAT pathway, the details of which are the subject of Proliferation #2: *Myeloproliferative Disorders*.

Myeloproliferation is the excess division and differentiation of progenitors. Progenitors have a limited number of divisions. When a myeloproliferative disorder provokes unregulated replication but doesn't induce malignant transformation, the bone marrow burns out, a process called **myelofibrosis**. When a myeloproliferative disorder provokes unregulated replication (which is a risk factor for acquiring new mutations) and does induce malignant transformation, the marrow first passes through **myelodysplasia**. Myelodysplasia shows expansion of a clonal cell type that overwhelms and crowds out the marrow. Myelodysplasia will become acute leukemia.

Lesson #3: Leukemia

While modern science has blurred the lines between lymphoma and leukemia, we unblur them. You are studying for a basic science exam, and to be a doctor, not a hematologist subspecialist. The only area of overlap you should feel uncomfortable with is CML, because CML is a myeloproliferative disorder (from the myeloid line) but is taught as a leukemia (combined with lymphoid leukemias). Leukemias are predominantly **leukocytes in the blood** (leuko, leukocyte; emia, in the blood). Leukemias can either be **chronic** (mature lymphocytes or mature neutrophils in the blood) or **acute** (immature blasts in the blood). Acute leukemias have acute presentations—high fever, bone pain, and pancytopenia of real cell lines. Chronic leukemias, because they are differentiated, do not have acute presentations, often presenting as an elevated white count without other symptoms. All leukemias crowd out the marrow, reducing other cell lines.

Chronic myelogenous leukemia is caused by the BCR-ABL gene fusion, known as the Philadelphia chromosome, caused by translocation t(9;22), which results in the BCR-ABL fusion protein, and is treated with the receptor tyrosine kinase inhibitor imatinib. This leukemia progresses to AML 70% of the time and ALL 30% of the time, as discussed in Proliferation #3: *Leukemia*. **Chronic lymphocytic leukemia** is a disease of the quite elderly, and is generally treated with watchful waiting, not needing to be treated, being caused not by a translocation but by a gene deletion.

Acute lymphocytic leukemia is the most common cancer in children. It is associated with translocation t(12;21). **Acute myelogenous leukemia** can occur from CML with t(9;22), called a blast crisis. However, other forms of AML exist that do not require first having CML. In particular, the M3 AML, **acute promyelocytic leukemia** (APL), develops from a t(15;17) translocation. APL is treated with all-trans retinoic acid. APL is unlike any of the AML variants, so we encourage you to learn APL as different from other AMLs.

Leukemoid reaction vs. leukemia. An elevated white count does not necessarily mean cancer. The white count elevates in infection and inflammation, and with steroid use. When there is an infection, there is a **left shift** or a **leukemoid reaction**, in which the white blood cell acutely rises as mature and immature cells are released. But "immature" in this case means bands, cells that are almost ready to be mature. A left shift is defined by cells on blood smear that are not quite mature. Because they are healthy cells, they will do what these cells are supposed to do. They will express **leukocyte alkaline phosphatase (LAP)**. Because the reaction is acute, there will be **no hepatosplenomegaly**. And because it is not cancer, there will be no **t(9;22)**. Leukemia, on the other hand, is not a response to an infection and won't go away (so has hepatosplenomegaly), is made from defective leukocytes (low LAP), and is made from cancer (has the Philadelphia chromosome). This is often tested, but we're not sure why. You get a CBC on someone. You got that CBC for a reason. If they are dyspneic and there is a pneumonia, the CBC shows bands, and the patient is infected. You treat the infection and the WBCs come down. No question it was infection. You get a CBC because the person has bone pain and fever, and is found to be pancytopenic with blasts on the smear. They have cancer.

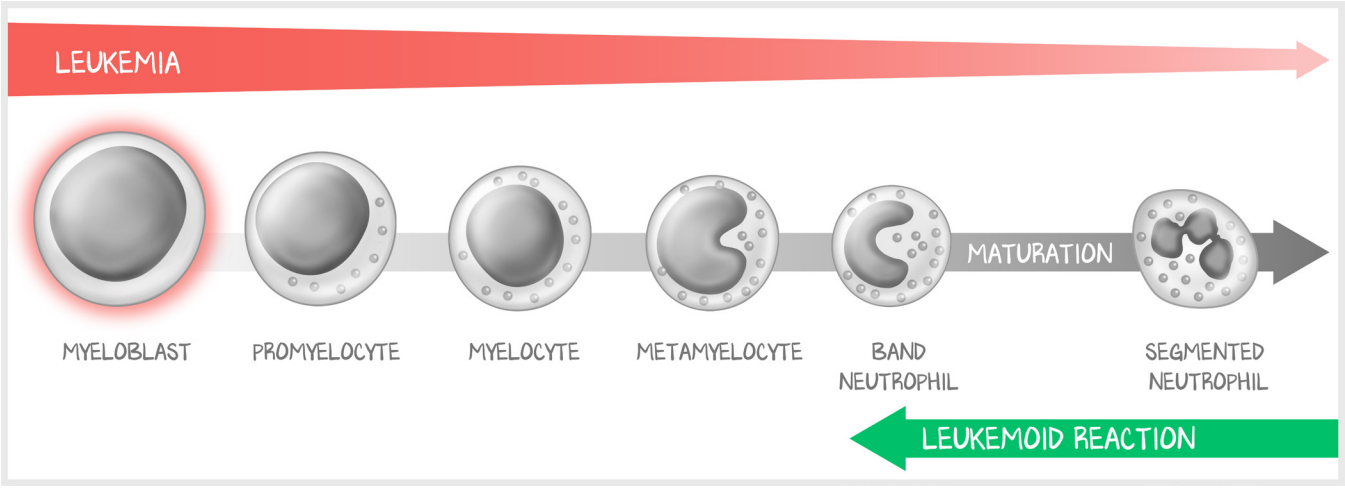

Figure 1.4: Leukemoid Reaction
We want you seeing "left shift infection" as "starting from the right," and leukemia as "starting on the left."

Lesson # 4: Lymphoma

Lymphoma, the tumor cells growing in a local mass and not in the blood, can either be B-cell lymphoma or T-cell lymphoma. B-cell lymphoma comes in the form of **Hodgkin's lymphoma** (with $CD15^+/CD30^+$, Reed-Sternberg cells) or **non-Hodgkin's lymphomas** (without $CD15^+/CD30^+$). There are histologic patterns that characterize more than one Hodgkin's lymphoma, but there is only one pathogenesis and one treatment, so we teach that there is one lymphoma with the Hodgkin's tag. All the other B-cell lymphomas are $CD15^-/CD30^-$ and have their own pathogenesis. Non-Hodgkin's lymphomas tend to be caused by a **translocation** event usually involving isotype switching, where the **Ig heavy chain** is connected to either a pro-growth or anti-apoptotic gene. Malignant transformation

with any of the translocations is commonly associated with EBV latency infection. A third of Hodgkin's lymphomas are caused by EBV as well. B-cell lymphomas usually involve the **lymph node** and are nearly the entire lesson (Proliferation #4: *Lymphoma*). When a patient presents with a painless swollen lymphadenopathy, you follow the same diagnostic pathway, and then are asked to know a little about the pathogenesis and histology.

$CD15^+/CD30^+$ B-CELL LYMPHOMAS	ALL OTHER B-CELL LYMPHOMAS	T-CELL LYMPHOMAS
Hodgkin's	Diffuse large B-cell lymphoma	Adult T-cell lymphoma (HLTV-1)
	Follicular lymphoma t(14;18)	Mycosis fungoides
	Mantle zone lymphoma t(11;14)	Sezary syndrome
	Marginal zone lymphoma t(11;18)	
	Burkitt's lymphoma (t8;14)	

Table 1.1: Lymphomas

T-cell lymphomas are much lower yield. They are associated with HTLV-1 and HHV-8 viruses. T cells tend to involve the skin. T-cell lymphoma gets an aside in Proliferation# 4: *Lymphoma*.

When you see "lymphoma," think "B-cell lymphoma" and decide between Hodgkin's or non-Hodgkin's.

Lesson #5: Plasma Cell Dyscrasias

While plasma cells are technically a lineage of terminally differentiated B lymphocytes, you should think of them as their own cell type and therefore a separate form of cancer. Plasma cells **secrete immunoglobulins** that cause symptoms. There are two main plasma cell dycrasias: **multiple myeloma**, which secretes light chains or IgG, causing lytic lesions, hypercalcemia, and renal failure; and **lymphoblastic lymphoma** (aka Waldenstrom's macroglobulinemia), which secretes IgM and causes hyperviscosity syndrome. Much of Proliferation #5: *Plasma Cell Dyscrasias* discusses the details of how multiple myeloma causes all the damage it does, and the spectrum from MGUS through plasma cell leukemia. Plasma cell dyscrasias are so unlike the rest of the proliferative disorders that you will not confuse them with other disorders that have the word lymphoma in them.